Patent
Attorney's Docket No. 016800-128

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Janusz CZERNIELEWSKI et al	Group Art Unit: 1205
Application No.: 08/765,064	Examiner: K. MacMillan
Filed: March 25, 1997	
For: DRUGS CONTAINING METRONIDAZOLE OR A SYNTHETIC MIXTURE OF METRONIDAZOLE AND CLINDAMYCIN	

REPLY AND AMENDMENTS PURSUANT TO
37 C.F.R. §§1.111, 1.115 and 1.119

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated June 3, 1997, kindly amend the above-identified application as follows:

IN THE CLAIMS:

Kindly cancel Claims 10 through 29, and substitute the following claims therefor:

--30. A method for the treatment of inflammation, said method comprising administering a composition which comprises an effective amount of metronidazole and clindamycin and a pharmaceutically acceptable carrier therefor.

31. A method for the treatment of inflammation, said method comprising topically administering a pharmaceutical composition comprising an anti-inflammatory effective amount of metronidazole and a topical pharmaceutically acceptable carrier therefor.

32. The method of Claim 30, wherein the amount of metronidazole present in said composition ranges from about 0.01% to 5% by weight with respect to the total weight of the pharmaceutical composition.

33. The method of Claim 31, wherein the amount of metronidazole present in said composition ranges from about 0.01% to 5% by weight with respect to the total weight of the pharmaceutical composition.

34. The method of Claim 30, where said treatment of inflammation comprises treatment of a skin disease.

35. The method of Claim 33, where said treatment of inflammation comprises treatment of a skin disease.

36. The method of Claim 34, wherein said skin disease is accompanied by dermatosis.

37. The method of Claim 35, where said skin disease is accompanied by dermatosis.

38. The method according to Claim 36, wherein said dermatosis is selected from the group consisting of eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

39. The method according to Claim 37, wherein said dermatosis is selected from the group consisting of eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

40. The method according to Claim 30, wherein said clindamycin is present in said composition in a proportion ranging from 0.01 % to 10% by weight with respect to the total weight of the composition.

41. The method according to Claim 33, wherein said clindamycin is present in said composition in a proportion ranging from 0.01 % to 10% by weight with respect to the total weight of the composition.

42. The method according to Claim 30, wherein the overall content of the metronidazole and clindamycin mixture does not exceed 5 to 10% of the total weight of said composition.

43. The method according to Claim 31, wherein the overall content of the metronidazole and clindamycin mixture does not exceed 5 to 10% of the total weight of said composition.--

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claims 10 through 29 have been cancelled in favor of new Claims 30 through 43. These amendments are made in order to expedite prosecution.

Upon entry of the subject amendments, all of the claims will be directed to a method for treating inflammation comprising administering a composition comprising an effective amount of metronidazole and clindamycin in combination with a pharmaceutically acceptable carrier, preferably by topical application. Based on the following, Applicants respectfully submit that these amendments should place this application in condition for allowance.

Turning to the Office Action, Applicants note at the outset that previous Claims 12-14, 16-17, 21-22, and 25 were objected to under 37 C.F.R. §1.75(c) as being of improper dependent form. The claims were indicated not to be further limiting because they only differed from the respective dependent claims by recitations of intended use. This objection should be moot based on the present amendment, which limits all of the claims to methods of treatment. Therefore, the recited intended uses comprise a proper claim limitation.

Also, all of the claims were rejected based on prior art. These rejections are respectfully traversed to the extent they may be applicable to the claims as amended. However, prior to specifically addressing the prior art, the present invention and its advantages are briefly summarized below.

The present invention generally relates to the use of metronidazole and clindamycin, in combination, for the treatment of inflammatory conditions, in particular those affecting the skin. As discussed in the subject application, metronidazole or 2-methyl-5-nitroimidazole-1-ethanol as it is also known, comprises known application for the treatment, topically, of acne rosacea as described, e.g., in U.S. Patent 4,837,378. However, while this compound effectively treats this condition, the exact mechanism which results in efficacy was poorly understood prior to the invention. It is well known, however, that this compound is an active anti-microbial

agent which is capable of killing certain anaerobic and parasitic infectious organisms.

The present inventors, quite surprisingly, have discovered that this compound exhibits potent anti-inflammatory activity, in particular when applied topically. Moreover, it has been surprisingly discovered that this compound, when combined with clindamycin, exhibits synergistic anti-inflammatory activity. This result is highly unexpected because clindamycin, like metronidazole, had recently been reported to possess activity as an antibiotic and, therefore, was commonly used in the treatment of acne by topical application thereof. However, this compound was not known to possess anti-inflammatory activity.

Based on the discovery of this synergistic activity, the present invention is directed to an effective means of treating inflammatory conditions, in particular those affecting the skin, comprising the application of a combination of metronidazole and clindamycin, e.g., by topical application to the skin. Skin diseases which may be treated with such a combination include, by way of example, eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

The synergistic anti-inflammatory results obtained by the combination of clindamycin and metronidazole may be appreciated upon review of the results contained in Example 1. This Example compares the anti-inflammatory effects of compositions

containing metronidazole alone, clindamycin alone, in relation to a composition containing a combination of metronidazole and clindamycin, present in the same amounts by weight. Specifically, these anti-inflammatory results were evaluated in a model of inflammation comprising oedema of the ear of the mouse which was induced by topical application of arachidonic acid. According to this model, topical application of arachidonic acid causes ear inflammation characterized by the rapid development of an oedema which becomes most pronounced about an hour after application.

This response may be quantified by measuring the thickness of the ear after treatment. Thus, compounds which inhibit inflammation in this model result in a reduction of oedema characterized by reduced thickness of the ear after application. The results obtained upon application of metronidazole alone, clindamycin alone, and a combination thereof, are summarized in the Table at page 8 of the subject application. These results clearly demonstrate that the application of clindamycin alone had no statistically significant effect on inflammation. In other words, it did not inhibit inflammation. By contrast, the 2% dosage of metronidazole alone resulted in 20% inhibition of inflammation after an hour and about 36% after two hours. Moreover, quite surprisingly, the combination of metronidazole and clindamycin resulted in 46% inhibition after an hour and 63% after two hours. Quite clearly, this enhancement in anti-inflammatory activity which occurred with the combination of

clindamycin and metronidazole could not have been predicted since clindamycin alone has no apparent affect on inflammation. Therefore, the present invention constitutes a patentable invention in the art, i.e., it provides a novel and non-obvious method of treating inflammation.

Turning now to the prior art rejections, Claim 10 was rejected under §102(b) as being anticipated by Borgman. This reference teaches a topical formulation comprising metronidazole for treatment of skin disorders. This rejection is moot as a topical composition containing metronidazole is no longer claimed. Withdrawal of this rejection is therefore respectfully requested.

Claims 10-25 were further rejected under 35 U.S.C. §102(b) as being anticipated by Busch et al, Chem. Abstracts AN 1976:145357. This reference teaches a composition comprising clindamycin and metronidazole. The reference further purportedly teaches the synergistic results of such a combination. However, Applicants respectfully submit that this reference fails to teach or suggest the claimed invention as the synergism observed by Busch et al relates to an anti-bacterial effect. Essentially, the reference purports that the association of clindamycin and metronidazole had a synergistic bacteriocidal effect, in particular against bacteroides fragilis. However, this reference fails to teach or suggest the claimed method of treatment, which is directed to the inhibition of the inflammation by the application of an asso-

ciation of clindamycin and metronidazole. Therefore, this reference fails to teach or suggest the claimed methods.

Claims 10-29 were further rejected under 35 U.S.C. §103 as being unpatentable over Ayer et al, U.S. Patent 4,018,918, taken in view of Borgman (WO 88/06888). Ayer et al is cited based on its disclosure pertaining to topical clindamycin preparations and their uses for treatment of skin disorders. The Examiner further notes that such compositions may comprise anti-inflammatories, in particular, steroidal anti-inflammatories. However, this reference completely fails to teach or suggest a composition comprising a combination of metronidazole and clindamycin, much less the use thereof for the treatment of inflammatory conditions.

Moreover, the deficiencies of Ayer et al are not cured by Borgman. This reference acknowledgedly teaches that metronidazole is an excellent topical anti-inflammatory which is suitable for usage in treatment of skin disorders such as acne. However, this reference contains non indication that clindamycin could potentiate the anti-inflammatory effects of this compound. Therefore, this reference also fails to teach or suggest the claimed invention.

Moreover, even assuming *arguendo* that there would have been motivation to have combined these compounds based on the fact that both had been reportedly useful for treatment of skin conditions, this rejection must be withdrawn based on the unexpected results which are achieved by the claimed invention.

As discussed above, it has been surprisingly discovered that the combination of clindamycin and metronidazole exhibit synergistic anti-inflammatory effects. Such synergism is not taught by any of the references cited by the Examiner, whether considered singularly or in combination. As discussed above, the only disclosure pertaining to synergistic activity of this combination relates to anti-microbial activity. In particular, as noted by the Examiner, it had been reported in the Busch et al Abstract that these compounds in combination exhibit greater anti-microbial activity, in particular, against bacteroides fragilis. However, such synergism would in no wise suggest that these compounds would exhibit synergistic anti-inflammatory activity. Indeed, this certainly could not have been expected given the fact that clindamycin by itself exhibits no such anti-inflammatory activity.

This absence of anti-inflammatory activity may be appreciated upon review of the results contained in Example 1. Therefore, based on the foregoing, there would have been no reason to have expected that such a combination would exhibit potent anti-inflammatory activity relative to either of these compounds used singularly. Therefore, withdrawal of the §103 rejection of Claims 10-29 based on Ayer et al taken in view of Borgman, alone, or in combination with the cited Abstracts relating to synergism, is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is re-

spectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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Date: December 3, 1997